Communication

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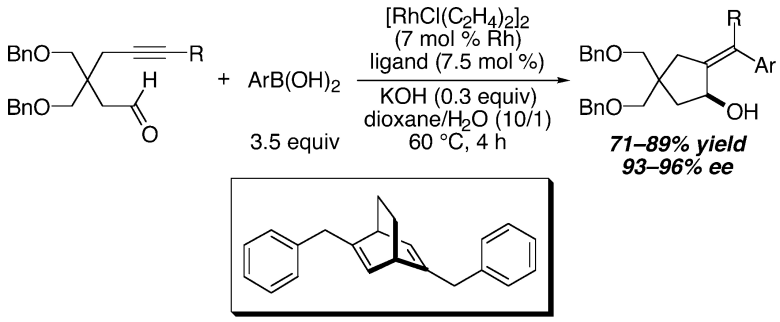

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Catalytic Asymmetric Arylative Cyclization of Alkynals: Phosphine-Free Rhodium/Diene Complexes as Efficient Catalysts

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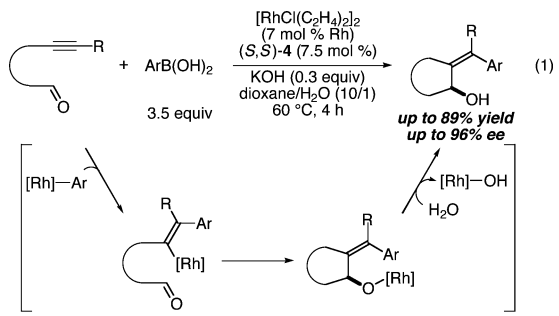
Transition metal-catalyzed tandem reactions involving multiple carbon−carbon bond formations are powerful methods for the preparation of structurally complex molecules in a convergent manner from relatively simple precursors.[1] For the construction of carbon−carbon bonds, a rhodium-catalyzed addition of organoboronic acids to unsaturated carbon−carbon or carbon−heteroatom bonds is a useful strategy,[2] due to the high functional-group compatibility and the ready availability and stability of organoboronic acids. Recently, several examples of rhodium-catalyzed tandem cyclization reactions with organoboron species have been described.[3] In addition to achieving the efficient assembly of molecular complexity, rhodium-catalyzed processes can also provide opportunities for asymmetric catalysis by employing appropriate chiral ligands.[3a,b]

To date, such rhodium-catalyzed multiple carbon−carbon bond-forming cyclization reactions using organoboron nucleophiles have been reported only in the context of 1,4-additions to α,β-unsaturated carbonyl compounds.[3,4] In this Communication, we describe that the addition/cyclization of arylboronic acids to alkynals proceeds smoothly by the use of a rhodium/diene catalyst, leading to cyclic allylic alcohols with a tetrasubstituted olefin;[5] at the same time, we have achieved effective asymmetric catalysis by the use of chiral diene ligands developed in our group (eq 1).

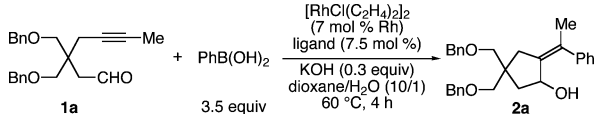


(1)

In an initial investigation, we employed alkynal **1a** as a model substrate in combination with $PhB(OH)_2$ to examine the effect of ligand in the presence of 7 mol % rhodium (Table 1). The use of bisphosphine ligands that are effective for the coupling of alkynes with organoboronic acids under rhodium catalysis[6] was found to be ineffective for this particular reaction (20−27% yield; entries 1−4).[7] The employment of PPh_3 as a ligand did not improve the reactivity either (20% yield; entry 5). In contrast to these results, the use of $[RhCl(cod)]_2$ as a catalyst with no addition of phosphine ligands in the presence of KOH efficiently promoted the reaction, leading to arylative cyclization product **2a** in good yield (73% yield; entry 6). To simplify the experimental manipulation, $[RhCl(cod)]_2$/KOH can be replaced by $[Rh(OH)(cod)]_2$, with a slight increase in the yield of **2a** (76% yield; entry 7).

Under these conditions with $[Rh(OH)(cod)]_2$ as a catalyst, several alkynals can be employed (Table 2), furnishing five- or six-membered cyclic allylic alcohols with a tetrasubstituted olefin in good to excellent yields (**2a**−**e**; 64−93% yield).[8] It is worth pointing out that this process can tolerate various functional groups such as ethers, esters, and sulfonamides.

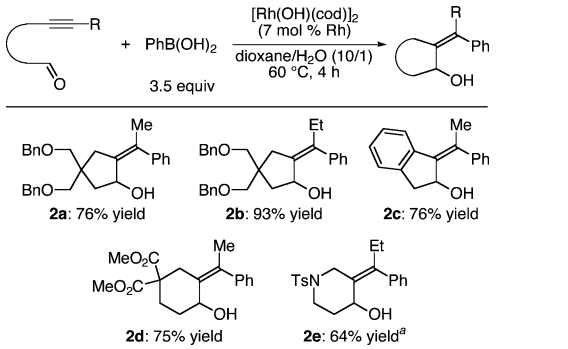
Table 1. Rhodium-Catalyzed Arylative Cyclization of Alkynal **1a** with Phenylboronic Acid: Ligand Effect



entry	ligand	yield (%)[a]
1	(*S*)-binap	24
2	dppp	23
3	dppb	20
4	dppf	27
5[b]	PPh_3	20
6[c]	cod	73
7[d]	cod	76

[a] Isolated yield. [b] Performed with 14 mol % ligand. [c] $[RhCl(cod)]_2$ was used as a catalyst. [d] $[Rh(OH)(cod)]_2$ was used as a catalyst without KOH.

Table 2. Rhodium-Catalyzed Arylative Cyclization: Scope of Alkynals



[a] Product was contaminated with unidentified impurity (5−10%).

For the development of an asymmetric variant of this process, it is easy to imagine that the employment of phosphorus-based chiral ligands is not suitable, because rhodium/phosphine complexes show low reactivity as demonstrated in Table 1. For example, the reaction of **1a** with $PhB(OH)_2$ in the presence of (*S*)-binap induces moderate stereoselectivity with very low yield of the product (24% yield, 76% ee; Table 3, entry 1). To overcome this reactivity problem in asymmetric catalysis, we utilized chiral norbornadiene ligand (*R*,*R*)-**3**,[9] effectively furnishing the arylative cyclization product in good yield with high enantioselectivity (76% yield, 94% ee; entry 2). A change of the ligand framework from bicyclo[2.2.1]heptadiene ((*R*,*R*)-**3**) to bicyclo[2.2.2]octadiene ((*S*,*S*)-**4**)[10] facilitates a slight increase in both yield and ee (78% yield, 95% ee; entry 3). Under these optimized conditions with (*S*,*S*)-**4**, various arylboronic acids

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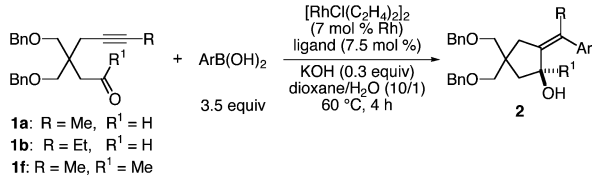
Table 3. Rhodium-Catalyzed Asymmetric Arylative Cyclization

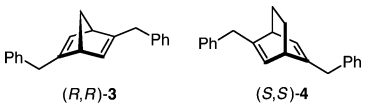


1a: R = Me, R^1 = H
1b: R = Et, R^1 = H
1f: R = Me, R^1 = Me

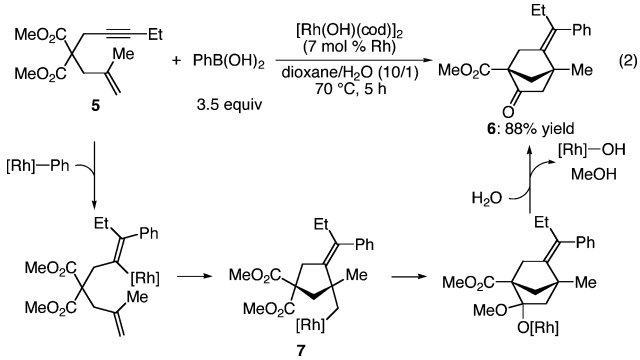
entry	substrate	Ar	ligand	product	yield (%)[a]	ee (%)[b]
1	**1a**	Ph	(*S*)-binap	**2a**	24	76 (*S*)[c]
2	**1a**	Ph	(*R*,*R*)-**3**	**2a**	76	94 (*R*)[c]
3	**1a**	Ph	(*S*,*S*)-**4**	**2a**	78	95 (*S*)[c]
4	**1b**	Ph	(*S*,*S*)-**4**	**2b**	89	94
5	**1a**	4-$MeOC_6H_4$	(*S*,*S*)-**4**	**2a-MeO**	71	93
6	**1a**	4-FC_6H_4	(*S*,*S*)-**4**	**2a-F**	77	93
7	**1a**	3-ClC_6H_4	(*S*,*S*)-**4**	**2a-Cl**	71	96
8	**1a**	2-naphthyl	(*S*,*S*)-**4**	**2a-Np**	78	96
9	**1f**	Ph	(*S*,*S*)-**4**	**2f**	89	75

[a] Isolated yield. [b] Ee was determined by HPLC on a Chiralpak AD-H column for entries 1−4, 6, and 9 and on a Chiralcel OD-H column for entries 5, 7, and 8. [c] Absolute configuration of the product was assigned by converting it to (*R*)-MTPA ester.

can be used to afford the products uniformly in high yield and stereoselection (71−89% yield, 93−96% ee; entries 4−8).[11] In addition, this process is also effective for alkynone substrates, which provide tertiary allylic alcohols with a tetrasubstituted olefin, in high yield with moderate ee (89% yield, 75% ee; entry 9).



Furthermore, 1,6-enynes are also suitable substrates for this arylative cyclization protocol by a rhodium/diene catalyst. For example, compound **5** undergoes the tandem cyclization to afford bicyclic compound **6** in 88% yield (eq 2). This process proceeds presumably through three sequential carbon−carbon bond-forming events via intermediate **7**. To the best of our knowledge, the conversion of **7** to **6** represents the first example of a ketone formation by the addition of an alkyl-rhodium species to an ester.[12]



In summary, we have developed a rhodium-catalyzed arylative cyclization of alkynals with arylboronic acids. While phosphorus-based ligands fail, the reaction has been successfully realized by the use of a diene ligand. In addition, by employing a chiral bicyclo-[2.2.2]octadiene ligand, we have efficiently coupled a range of arylboronic acids with these substrates in very good enantiomeric excess. We have further demonstrated that other substrates such as alkynones and enynes can also undergo multiple carbon−carbon bond-forming reactions under rhodium/diene catalysis. Future studies will explore further development of chiral diene ligands and their application to various transition metal-catalyzed asymmetric processes.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) These reactions with bisphosphine ligands typically result in the recovery of unreacted alkynal **1a** as the major component.

(8) To date, we have not been able to achieve intermolecular three-component couplings of organoboronic acids, alkynes, and aldehydes.

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(11) Alkylboronic acids are not suitable nucleophiles under the same reaction conditions.

(12) See refs 3c and 3d for intramolecular insertion of alkyl-rhodium species to electron-deficient olefins.

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